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Date: March 14, 2003

Box Provisional-Application
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Sir:

Enclosed please find a provisional application for United States patent as identified below:

Inventor/s (ALL inventors, including NAME, plus city and state of RESIDENCE for each):

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Title: SUBSTITUTED ANILINE DERIVATIVES

PROVISIONAL PATENT APPLICATION COVER SHEET

including the items indicated:

1. Specification and claims (21 pp.)
   claims: 1 indep.; 20 dep.; X multiple dep.

2. [X] Check in the amount of $160.00, ($160 filing; $0 recording)

Respectfully submitted,

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Substituted aniline derivatives

Field of the invention

The present invention relates to novel substituted aniline derivatives being openers of the KCNQ family potassium ion channels. The compounds are useful for the prevention, treatment and inhibition of disorders and diseases being responsive to opening of the KCNQ family potassium ion channels, one such disease is epilepsy.

Background of the invention

Ion channels are cellular proteins that regulate the flow of ions, including potassium, calcium, chloride and sodium into and out of cells. Such channels are present in all animal and human cells and affect a variety of processes including neuronal transmission, muscle contraction, and cellular secretion.

Humans have over 70 potassium channel subtypes (Jentsch *Nature Reviews Neuroscience* **2000**, 1, 21-30) with a great diversity with regard to both stucture and function. Neuronal potassium channels, which are found in the brain, are primarily responsible for maintaining a negative resting membrane potential, as well as controlling membrane repolarisation following an action potential.

One subset of potassium channel genes is the KCNQ family. Mutations in four out of five KCNQ genes have been shown to underlie diseases including cardiac arythmias, deafness and epilepsy (Jentsch *Nature Reviews Neuroscience* **2000**, 1, 21-30).

The KCNQ4 gene is thought to encode a potassium channel found in outer hair cells of the cochlea, mutations in this gene can lead to a form of inherited deafness. KCNQ1 (KvLTQ1) is co-assembled with the product of the KCNE1 (minimal K(+)-channel protein) gene in the heart to form a cardiac-delayed rectifier-like K(+) current. Mutations in this channel can cause one form of inherited long QT syndrome (LQT1), as well as being associated with a form of deafness (Robbins *Pharmacol Ther* **2001**, 90, 1-19).

The genes KCNQ2 and KCNQ3 were discovered in 1988 and appear to be mutated in a rare inherited form of benign familial neonatal convulsions (Rogawski *Trends in*

Neurosciences **2000**, 23, 393-398). The proteins encoded by the KCNQ2 and KCNQ3 genes are localised in the pyramidal neurons of the human cortex and hippocampus, regions of the brain associated with seizure generation and propagation (Cooper et al. *Proceedings National Academy of Science U S A* **2000**, 97, 4914-4919).

KCNQ2 and KCNQ3 are two potassium channel subunits that form "M-currents" when expressed in vitro. The M-current is a non-inactivating potassium current found in many neuronal cell types. In each cell type, it is dominant in controlling membrane excitability by being the only sustained current in the range of action potential initiation (Marrion *Annual Review Physiology* **1997**, 59, 483-504). Modulation of the M-current has dramatic effects on neuronal excitability, for example activation of the current will reduce neuronal excitability. Thus openers of these channels, or activators of the M-current, may be of use in the treatment of disorders of neuronal hyperexcitability including convulsive disorders, epilepsy and neuropathic pain.

Retigabine (D-23129; N-(2-amino-4-(4-fluorobenzylamino)-phenyl) carbamic acid ethyl ester) and analogues thereof are disclosed in EP554543. Retigabine is an antiepileptic compound with a broad spectrum of action and potent anticonvulsant properties, both in vitro and in vivo. It is active after oral and intraperitoneal administration in rats and mice in a range of anticonvulsant tests including: electrically induced seizures, seizures induced chemically by pentylenetetrazole, picrotoxin and N-methyl-D-aspartate (NMDA) and in a genetic animal model, the DBA/2 mouse (Rostock et al. *Epilepsy Research* **1996**, 23, 211-223). In addition, retigabine is active in the amygdala kindling model of complex partial seizures, further indicating that this compound has potential for antiepileptic therapy. In clinical trials, retigabine has recently shown effectiveness in reducing the incidence of seizures in epileptic patients (Bialer et al. *Epilepsy Research* **2002**, 51, 31-71).

Retigabine has been shown to activate a K(+) current in neuronal cells and the pharmacology of this induced current displays concordance with the published pharmacology of the M-channel, which recently was correlated to the KCNQ2/3 K(+) channel heteromultimere. This suggests that activation of KCNQ2/3 channels may be responsible for some of the anticonvulsant activity of this agent (Wickenden et al.

Molecular Pharmacology **2000**, 58, 591-600) – and that other agents working by the same mechanism may have similar uses.

KCNQ channels have also been reported to be upregulated in models of neuropathic pain (Wickenden et al. *Society for Neuroscience Abstracts* **2002**, 454.7), and potassium channel modulators have been hypothesised to be active in both neuropathic pain and epilepsy (Schroder et al. *Neuropharmacology* **2001**, 40, 888-898).

Retigabine has also been shown to be beneficial in animal models of neuropathic pain (Blackburn-Munro and Jensen *European Journal of Pharmacology* **2003**, 460, 109-116), thus we suggest that openers of KCNQ channels will be of use in treating pain disorders including neuropathic pain.

Finally, retigabine and KCNQ modulators may exhibit protection against the neurodegenerative aspects of epilepsy, as retigabine has been shown to prevent limbic neurodegeneration and the expression of markers of apoptosis following kainic acid-induced status epilepticus in the rat (Ebert et al. *Epilepsia* **2002**, 43 Suppl 5, 86-95). This may have relevance for preventing the progression of epilepsy in patients, i.e. be anti-epileptogenic. Retigabine has also been shown to delay the progression of hippocampal kindling in the rat, a further model of epilepsy development (Tober et al. *European Journal Of Pharmacology* **1996**, 303, 163-169).

Thus we suggest that these properties of retigabine and KCNQ modulators may prevent neuronal damage induced by excessive neuronal activation, and may be of use in the treatment of neurodegenerative diseases, and be disease modifying (or antiepileptogenic) in patients with epilepsy.

WO01/022953 describes the use of retigabine for prophylaxis and treatment of neuropathic pain such as allodynia, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathie and neuropathic pain related to migraine.

WO02/049628 describes the use of retigabine for the prevention, treatment, inhibition and amelioration of anxiety-related conditions such as anxiety, generalized anxiety

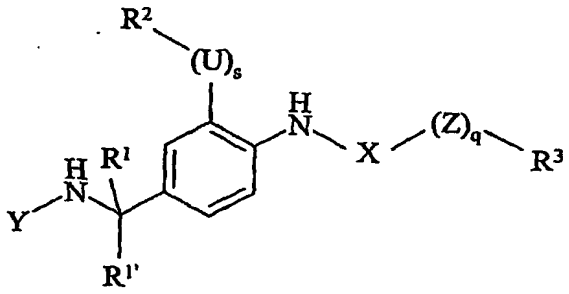
disorder, panic anxiety, obsessive compulsive disorder, social phobia, performance anxiety, post-traumatic stress disorder, acute stress reaction, adjustment disorders, hypochondriacal disorders, separation anxiety disorder, agoraphobia and specific phobias.

WO97/15300 describes the use of retigabine for the treatment of neurodegenerative disorders such as alzheimer's disease; huntington's chorea; multiple sclerosis; amyotrophic lateral sclerosis; Creutzfeld-Jakob disease; Parkinson's disease; encephalopathies induced by AIDS or infection by rubella viruses, herpes viruses, borrelia and unknown pathogens; trauma-induced neurodegenerations; neuronal hyperexcitation states such as in medicament withdrawal or intoxication; and neurodegenerative diseases of the peripheral nervous system such as polyneuropathies and polyneuritides.

Summary of the invention

One object of the present invention is to provide novel compounds, which are potent openers of the KCNQ family potassium channels.

Accordingly, the present invention relates to substituted aniline derivatives of the general formula I



(I)

wherein

U is O, S or $NR^{2'}$;

s is 0 or 1;

X is CO or SO_2;

Z is O, S or NR^4, wherein R^4 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

q is 0 or 1;

R^1 and $R^{1'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl;

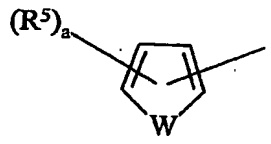
R^2 is selected from the group consisting of hydrogen, halogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl and cyano; provided that when R^2 is halogen or cyano then s is 0;

when s is 1 and **U** is $NR^{2'}$ then $R^{2'}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl; or R^2 and $R^{2'}$ together form a 5-8 membered saturated or unsaturated ring which optionally contains one further heteroatom;

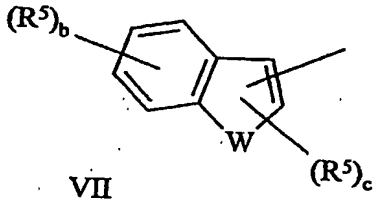
R^3 is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl;

and

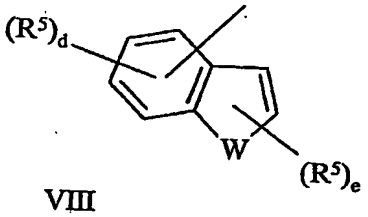
Y represents a group of formula VI, VII, VIII, IX or X:



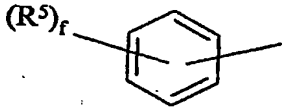
VI



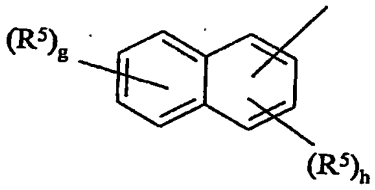
VII



VIII



IX



X

wherein

the line represents a bond attaching the group represented by Y to the nitrogen atom;

W is O or S;

a is 0, 1, 2 or 3;

b is 0, 1, 2, 3 or 4;

c is 0 or 1;

d is 0, 1, 2 or 3;

e is 0, 1 or 2;

f is 0, 1, 2, 3, 4 or 5;

g is 0, 1, 2, 3 or 4;

h is 0, 1, 2 or 3; and

each R^5 is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(an/en/yn)yloxy, halogen, halo-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, nitro, -$NR^7R^{7'}$, -S-R^8, -SO_2R^8 and SO_2OR^8, or two substituents together form a 5-8 membered saturated or unsaturated ring which optionally contains one or two heteroatoms;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar;

R^7 and $R^{7'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and acyl; and

R^8 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and $-NR^9R^{9'}$; wherein R^9 and $R^{9'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; with the provisos that when R^5 is SO_2OR^8 then R^8 is not $-NR^9R^{9'}$ and when R^5 is SO_2R^8 then R^8 is not a hydrogen atom.

or salts thereof.

Detailed description

One embodiment of the invention relates to compounds of the general formula I, wherein $\mathbf{R^1}$ and $\mathbf{R^{1'}}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

In another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^1}$ and $\mathbf{R^{1'}}$ are independently selected from the group consisting of acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl.

One embodiment of the invention relates to compounds of the general formula I, wherein $\mathbf{R^1}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and $\mathbf{R^{1'}}$ is selected from the group consisting of acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein one of $\mathbf{R^1}$ and $\mathbf{R^{1'}}$ is a hydrogen atom.

In a preferred embodiment, the invention relates to compounds of formula I, wherein both $\mathbf{R^1}$ and $\mathbf{R^{1'}}$ are hydrogen atoms.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1.

In a preferred embodiment, the invention relates to compounds of formula I, wherein s is 0.

In yet another embodiment, the invention relates to compounds of the general formula I, wherein $\mathbf{R^2}$ is selected from the group consisting of Ar, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of the general formula I, wherein R^2 is selected from the group consisting of hydrogen, halogen, cyano, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl and Ar-C_{3-8}-cycloalk(en)yl; provided that when R^2 is halogen or cyano then s is 0.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^2 is C_{1-6}-alk(en/yn)yl, typically C_{1-3}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^2 is C_{3-8}-cycloalk(en)yl, typically C_{3-6}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^2 is C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, typically C_{3-6}-cycloalk(en)yl-C_{1-3}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^2 is Ar-C_{1-6}-alk(en/yn)yl, typically Ar-C_{1-3}-alk(en/yn)yl.

In a preferred embodiment, the invention relates to compounds of the general formula I, wherein R^2 is Ar-C_{3-8}-cycloalk(en)yl, typically Ar-C_{3-6}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 0 and R^2 is different from a hydrogen atom, a halogen atom and C_{1-6}-alkyl.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, U is O and R^2 is different from a hydrogen atom, C_{1-6}-alkyl and acyl.

In yet another embodiment, the invention relates to compounds of the general formula I, wherein s is 1, U is S or $NR^{2'}$ and R^2 is a hydrogen atom.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 0 and R^2 is cyano.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 0 and $\mathbf{R^2}$ is a halogen atom.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1 and **U** is O or S.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1 and **U** is $NR^{2'}$.

In yet another embodiment, the invention relates to compounds of the general formula I, wherein s is 1, **U** is $NR^{2'}$ and $\mathbf{R^{2'}}$ is selected from the group consisting of Ar, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of the general formula I, wherein s is 1, **U** is $NR^{2'}$and $\mathbf{R^{2'}}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl and Ar-C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of the general formula I, wherein s is 1, **U** is $NR^{2'}$and $\mathbf{R^2}$ and $\mathbf{R^{2'}}$ together form a 5-8 membered saturated or unsaturated ring which optionally contains one further heteroatom.

In yet another embodiment, the invention relates to compounds of formula I, wherein $\mathbf{R^2}$ and $\mathbf{R^{2'}}$ together form pyrrolidin, piperidin, piperazin, morpholin, pyrrol, oxazolidin, thiazolidin or imidazolidin.

In yet another embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is $NR^{2'}$ and $\mathbf{R^{2'}}$ is a hydrogen atom.

In a preferred embodiment, the invention relates to compounds of formula I, wherein s is 1, **U** is $NR^{2'}$ and both $\mathbf{R^2}$ and $\mathbf{R^{2'}}$ are hydrogen atoms.

In yet another embodiment, the invention relates to compounds of formula I, wherein **s** is 1, **U** is $NR^{2'}$ and at least one of R^2 and $R^{2'}$ is different from Ar, Ar-C_{1-6}-alk(en/yn)yl and Ar-C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is SO_2.

In a preferred embodiment, the invention relates to compounds of formula I, wherein **X** is CO.

In yet another embodiment, the invention relates to compounds of formula I, wherein **q** is 0.

In a preferred embodiment, the invention relates to compounds of formula I, wherein **q** is 1.

In yet another embodiment, the invention relates to compounds of formula I, wherein **Z** is S or NR^4.

In a preferred embodiment, the invention relates to compounds of formula I, wherein **Z** is O.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^3 is selected from the group consisting of Ar, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^3 is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl and Ar-C_{3-8}-cycloalk(en)yl.

One embodiment of the invention relates to compounds of the general formula I, wherein R^3 is Ar; with the proviso that Ar is different from optionally substituted phenyl, optionally substituted condensed phenyl and optionally substituted thienyl.

One embodiment of the invention relates to compounds of the general formula I, wherein R^3 is Ar-C_{1-6}-alk(en/yn)yl; with the proviso that Ar-C_{1-6}-alk(en/yn)yl is different from optionally substituted phenyl-C_{1-6}-alk(en/yn)yl, optionally substituted condensed phenyl-C_{1-6}-alk(en/yn)yl, and optionally substituted condensed phenyl-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of the general formula I, wherein **Y** is different from optionally substituted thienyl or phenyl when R^3 is Ar-C_{1-6}-alkyl, wherein Ar is optionally substituted naphtyl and C_{1-6}-alkyl is vinylene, 1-propenylene, methylene or ethylene.

In yet another embodiment, the invention relates to compounds of the general formula I, wherein **Y** is optionally substituted thienyl or phenyl when R^3 is different from Ar-C_{1-6}-alkyl, wherein Ar is optionally substituted naphtyl and C_{1-6}-alkyl is vinylene, 1-propenylene, methylene or ethylene.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 0 and R^3 is different from C_{1-4}-alkyl, acyl and phenyl optionally being substituted by hydroxyl or C_{1-4}-alkanyloxy.

In yet another embodiment, the invention relates to compounds of formula I, wherein **X** is CO, **q** is 0 and R^3 is C_{1-6}-alk(en/yn)yl, with the proviso that R^3 is different from a methyl group.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^3 is C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

In a preferred embodiment, the invention relates to compounds of formula I, wherein R^3 is C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^3 is ethyl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^3 is isopropyl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^3 is isopropylmethyl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^3 is *tert*-butylmethyl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^3 is Ar-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein R^3 is Ar-methyl.

In yet another embodiment, the invention relates to compounds of formula I, wherein each R^5 is independently selected from the group consisting of Ar-C_{1-6}-alk(en/yn)yl, acyl, -CO-$NR^6R^{6'}$, cyano, nitro, -$NR^7R^{7'}$, -S-R^8, -SO_2R^8 and SO_2OR^8.

In yet another embodiment, the invention relates to compounds of formula I, wherein each R^5 is independently selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, halogen, halo-C_{1-6}-alk(en/yn)yl and C_{1-6}-alk(an/en/yn)yloxy; or two R^5 together form a 5-8 membered saturated or unsaturated ring which optionally contains one or two heteroatoms.

In a preferred embodiment, the invention relates to compounds of formula I, wherein each R^5 is independently selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar, halogen, halo-C_{1-6}-alk(en/yn)yl and C_{1-6}-alk(an/en/yn)yloxy; or two R^5 together form a 5-8 membered saturated or unsaturated ring which optionally contains one or two heteroatoms.

In yet another embodiment, the invention relates to compounds of formula I, wherein each R^5 is independently selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar, halogen, halo-C_{1-6}-alk(en/yn)yl and C_{1-6}-alk(an/en/yn)yloxy.

In yet another embodiment, the invention relates to compounds of formula I, wherein two adjacent R^5 together form a 5-8 membered saturated or unsaturated ring which optionally contains one or two heteroatoms.

In yet another embodiment, the invention relates to compounds of formula I, wherein two adjacent R^5 together form a 5-8 membered saturated or unsaturated carbocyclic ring.

In yet another embodiment, the invention relates to compounds of formula I, wherein two adjacent R^5 together form
$-(CH_2)_{n*}-CH_2-$, $-CH=CH-(CH_2)_{m*}-$, $-CH_2-CH=CH-(CH_2)_{p*}$,
$-(CH_2)_{n*}-O-$, $-O-(CH_2)_{m*}-O-$, $-CH_2-O-(CH_2)_{p*}-O-$, $-CH_2-O-CH_2-O-CH_2-$,
$-(CH_2)_{n*}-S-$, $-S-(CH_2)_{m*}-S-$, $-CH_2-S-(CH_2)_{p*}-S-$, $-CH_2-S-CH_2-S-CH_2-$,
$-(CH_2)_{n*}-NH-$, $-NH-(CH_2)_{m*}-NH-$, $-CH_2-NH-(CH_2)_{p*}-NH-$, $-CH=CH-NH-$,
$-O-(CH_2)_{m*}-NH-$, $-CH_2-O-(CH_2)_{p*}-NH-$ or $-O-(CH_2)_{p*}-NH-CH_2-$, $-S-(CH_2)_{m*}-NH-$,
$-N=CH-NH-$, $-N=CH-O-$ or $-N=CH-S-$, wherein m* is 1, 2 or 3, n* is 2, 3 or 4 and p* is 1 or 2.

In yet another embodiment, the invention relates to compounds of formula I, wherein two adjacent R^5 together form $-(CH_2)_{n*}-CH_2-$, $-CH=CH-(CH_2)_{m*}-$, $-CH_2-CH=CH-(CH_2)_{p*}$, wherein m* is 1, 2 or 3, n* is 2, 3 or 4 and p* is 1 or 2.

In yet another embodiment, the invention relates to compounds of formula I, wherein two adjacent R^5 together form $-(CH_2)_{n*}-CH_2-$ wherein n* is 2, 3 or 4.

In yet another embodiment, the invention relates to compounds of formula I, wherein one R^5 is a halogen atom.

In yet another embodiment, the invention relates to compounds of formula I, wherein two substituents R^5 are independently selected halogen atoms.

In yet another embodiment, the invention relates to compounds of formula I, wherein one R^5 is C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein one R^5 is halo-C_{1-6}-alk(en/yn)yl.

In yet another embodiment, the invention relates to compounds of formula I, wherein one R^5 is C_{3-8}-cycloalk(en)yl.

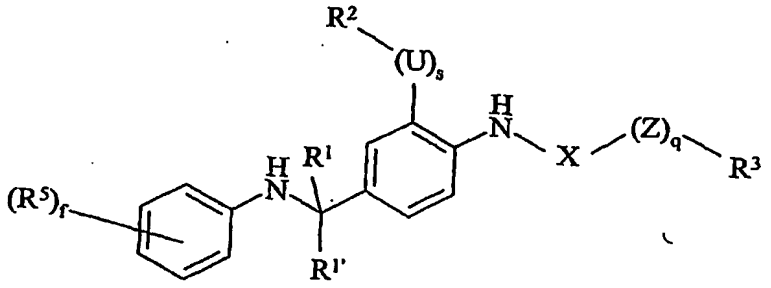
In yet another embodiment, the invention relates to compounds of formula I, wherein one R^5 is Ar.

In yet another embodiment, the invention relates to compounds of formula I, wherein one R^5 is C_{1-6}-alk(en/yn)yloxy.

In yet another embodiment, the invention relates to compounds of formula I, wherein two adjacent R^5 form a 5-8 membered saturated carbocyclic ring.

The molecular weight of the compounds of the invention may vary from compound to compound.The molecular weight of a compound of formula I is typically more than 200 and less than 600, and more typically more than 250 and less than 550.

One aspect of the invention, relates to compounds of general formula XI and salts thereof:



(XI)

wherein f, s, q, U, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9 and $R^{9'}$ are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XI.

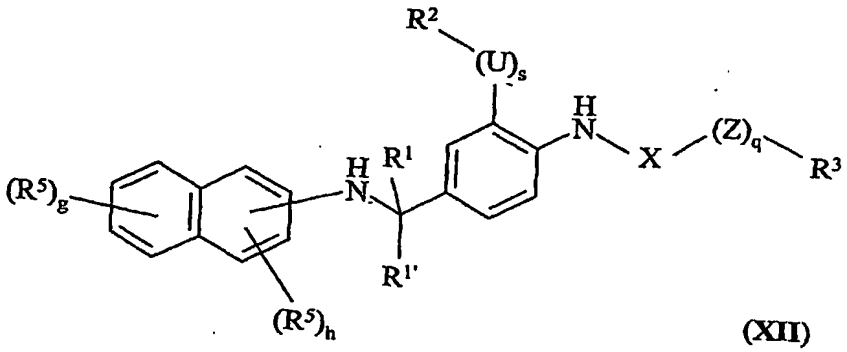
In another embodiment, the invention relates to compounds of the general formula XI, which is not substituted by R^5.

In another embodiment, the invention relates to compounds of the general formula XI being monosubstituted by R^5, such as in the ortho-, meta- or para-position.

In yet another embodiment, the invention relates to compounds of the general formula XI being disubstituted by R^5, such as in the ortho- and para-position, in the metha- and para-position and in the orto- and meta-position.

In yet another embodiment, the invention relates to compounds of the general formula XI being trisubstituted by R^5.

Another aspect of the invention relates to compounds of the general formula XII or salts thereof:



(XII)

wherein g, h, s, q, U, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9 and $R^{9'}$ are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XII.

In an embodiment, the invention relates to compounds of the general formula XII, wherein the nitrogen atom is attached to position 1 of the naphtyl group.

In another embodiment, the invention relates to compounds of the general formula XII, wherein the nitrogen atom is attached to position 2 of the naphtyl group.

In yet another embodiment, the invention relates to compounds of the general formula XII, wherein g is 0, 1, 2 or 3, typically 0, 1 or 2.

In yet another embodiment, the invention relates to compounds of the general formula XII, wherein h is 0, 1 or 2, typically 0 or 1.

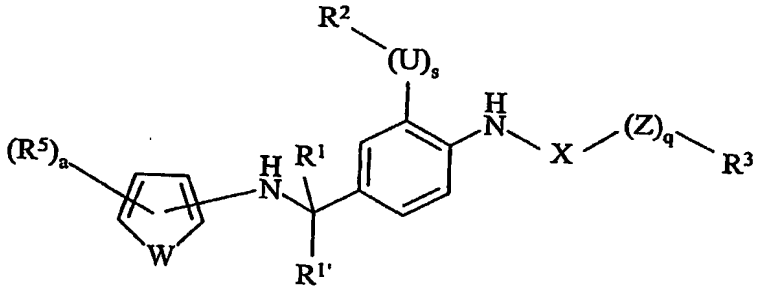
In yet another embodiment, the invention relates to compounds of the general formula XII, which are not substituted by R^5.

In yet another embodiment, the invention relates to compounds of the general formula XII being monosubstituted by R^5.

In yet another embodiment, the invention relates to compounds of the general formula XII being disubstituted by R^5.

In yet another embodiment, the invention relates to compounds of the general formula XII being trisubstituted by R^5.

Yet another aspect of the invention relates to compounds of the general formula XIII or salts thereof:



(XIII)

wherein a, s, q, U, W, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9 and $R^{9'}$ are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XIII.

In an embodiment, the invention relates to compounds of the general formula XIII, wherein the nitrogen atom is attached to position 2 of the heteroaromatic group.

In another embodiment, the invention relates to compounds of the general formula XIII, wherein the nitrogen atom is attached to position 3 of the heteroaromatic group.

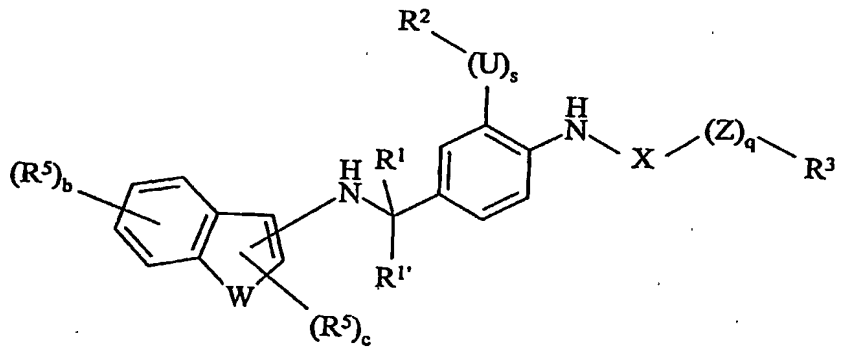
In yet another embodiment, the invention relates to compounds of the general formula XIII, wherein a is 0, 1 or 2.

In yet another embodiment, the invention relates to compounds of the general formula XIII, which are not substituted by $\mathbf{R^5}$.

In yet another embodiment, the invention relates to compounds of the general formula XIII being monosubstituted by $\mathbf{R^5}$.

In yet another embodiment, the invention relates to compounds of the general formula XIII being disubstituted by $\mathbf{R^5}$.

Yet another aspect of the invention relates to compounds of the general formula XIV or salts thereof:



(XIV)

wherein **b, c, s, q, U, W, X, Z,** $\mathbf{R^1}$, $\mathbf{R^{1'}}$, $\mathbf{R^2}$, $\mathbf{R^{2'}}$, $\mathbf{R^3}$, $\mathbf{R^4}$, $\mathbf{R^5}$, $\mathbf{R^6}$, $\mathbf{R^{6'}}$, $\mathbf{R^7}$, $\mathbf{R^{7'}}$, $\mathbf{R^8}$, $\mathbf{R^9}$ and $\mathbf{R^{9'}}$ are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XIV.

In an embodiment, the invention relates to compounds of the general formula XIV, wherein the nitrogen atom is attached to position 2 of the heteroaromatic group.

In another embodiment, the invention relates to compounds of the general formula XIV, wherein the nitrogen atom is attached to position 3 of the heteroaromatic group.

In yet another embodiment, the invention relates to compounds of the general formula XIV, wherein **b** is 0, 1, 2 or 3, typically 0, 1 or 2.

In yet another embodiment, the invention relates to compounds of the general formula XIV, wherein **c** is 0 or 1, typically 0.

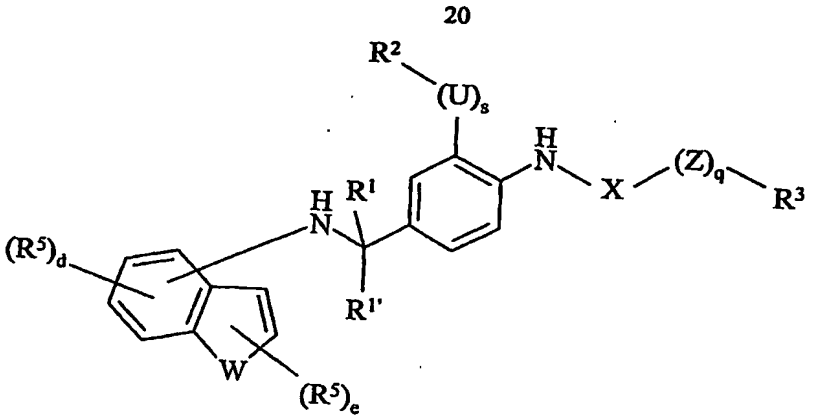
In yet another embodiment, the invention relates to compounds of the general formula XIV, which is not substituted by $\mathbf{R^5}$.

In yet another embodiment, the invention relates to compounds of the general formula XIV being monosubstituted by $\mathbf{R^5}$.

In yet another embodiment, the invention relates to compounds of the general formula XIV being disubstituted by $\mathbf{R^5}$.

In yet another embodiment, the invention relates to compounds of the general formula XIV being trisubstituted by $\mathbf{R^5}$.

Yet another aspect of the invention relates to compounds of the general formula XV or salts thereof:



(XV)

wherein **d, e, s, q, U, W, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9** and **$R^{9'}$** are as defined under formula I. Any of the embodiments related to formula I are also embodiments of formula XV.

In an embodiment, the invention relates to compounds of the general formula XV, wherein the nitrogen atom is attached to position 4 of the heteroaromatic group.

In another embodiment, the invention relates to compounds of the general formula XV, wherein the nitrogen atom is attached to position 5 of the heteroaromatic group.

In an embodiment, the invention relates to compounds of the general formula XV, wherein the nitrogen atom is attached to position 6 of the heteroaromatic group.

In another embodiment, the invention relates to compounds of the general formula XV, wherein the nitrogen atom is attached to position 7 of the heteroaromatic group.

In yet another embodiment, the invention relates to compounds of the general formula XV, wherein **d** is 0, 1 or 2, typically 0 or 1.

In yet another embodiment, the invention relates to compounds of the general formula XV, wherein **e** is 0 or 1.

In yet another embodiment, the invention relates to compounds of the general formula XV, which is not substituted by R^5.

In yet another embodiment, the invention relates to compounds of the general formula XV being monosubstituted by R^5.

In yet another embodiment, the invention relates to compounds of the general formula XV being disubstituted by R^5.

In yet another embodiment, the invention relates to compounds of the general formula XV being trisubstituted by R^5.

The compounds of the following list and salts thereof are preferred:

1a {2-Amino-4-[(4-tert-butylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1b (2-Amino-4-phenylaminomethyl-phenyl)-carbamic acid ethyl ester

1c [2-Amino-4-(naphthalen-2-ylaminomethyl)-phenyl]-carbamic acid ethyl ester

1d [2-Amino-4-(p-tolylamino-methyl)-phenyl]-carbamic acid ethyl ester

1e {2-Amino-4-[(4-trifluoromethylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1f {2-Amino-4-[(4-chlorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1g {2-Amino-4-[(3-fluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1h {2-Amino-4-[(4-fluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1i {2-Amino-4-[(2-fluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1j [2-Amino-4-(biphenyl-4-ylaminomethyl)-phenyl]-carbamic acid ethyl ester

1k {2-Amino-4-[(2,4-difluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1l {2-Amino-4-[(4-methoxyphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1m {2-Amino-4-[(4-cyclohexylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1n [2-Amino-4-(indan-5-ylaminomethyl)-phenyl]-carbamic acid ethyl ester

1o {2-Amino-4-[(4-isopropylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1p {2-Amino-4-[(4-butylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

According to one embodiment, the invention relates to a pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a compound of formula I wherein s, q, U, X, Z, Y, W, R^4, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9 and $R^{9'}$ are as defined under formula I, or salts thereof.

According to one embodiment, the invention relates to a pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a compound of formula XI wherein **f, s, q, U, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9** and **$R^{9'}$** are as defined under formula XI, or salts thereof.

According to one embodiment, the invention relates to a pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a compound of formula XII wherein **g, h, s, q, U, X, Z, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9** and **$R^{9'}$** are as defined under formula XII, or salts thereof.

According to one embodiment, the invention relates to a pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a compound of formula XIII wherein **a, s, q, U, X, Z, W, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9** and **$R^{9'}$** are as defined under formula XIII, or salts thereof.

According to one embodiment, the invention relates to a pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a compound of formula XIV wherein **b, c, s, q, U, X, Z, W, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9** and **$R^{9'}$** are as defined under formula XIV, or salts thereof.

According to one embodiment, the invention relates to a pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a compound of formula XV wherein **d, e, s, q, U, X, Z, W, R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, R^4, R^5, R^6, $R^{6'}$, R^7, $R^{7'}$, R^8, R^9** and **$R^{9'}$** are as defined under formula XV, or salts thereof.

The invention provides a pharmaceutical composition for oral or parenteral administration, said pharmaceutical composition comprising at least one compound of formula I or a salt thereof in a therapeutically effective amount together with one or more pharmaceutically acceptable carriers or diluents.

In one aspect, the compounds of the invention may be administered as the only therapeutically effective compound.

In another aspect the compounds of the invention may be administered as a part of a combination therapy, i.e. the compounds of the invention may be administered in combination with other therapeutically effective compounds having e.g. anti-epileptic properties. The effects of such other compounds having anti-epileptic properties may include but not be limited to activities on:

- ion channels such as sodium, potassium, or calcium channels
- the excitatory amino acid systems e.g. blockade or modulation of NMDA receptors
- the inhibitory neurotransmitter systems e.g. enhancement of GABA release, or blockade of GABA-uptake and/or
- membrane stabilisation effects.

Current antiepileptic medications include, but are not limited to, tiagabine, carbamazepine, sodium valproate, lamotrigine, gabapentin, pregabalin, ethosuximide, levetiracetam, phenytoin, topiramate, zonisamide as well as members of the benzodiazepine and barbiturate class.

In one aspect, the compounds of the invention have been found to have effect on potassium channels of the KCNQ family, in particular the KCNQ2 subunit.

The compounds of the invention are considered useful for increasing ion flow in a voltage-dependent potassium channel.

The compounds of the invention are considered useful for the prevention, treatment or inhibition of a disorder or condition being responsive to an increased ion flow in a potassium channel such as the KCNQ family potassium ion channels.

Accordingly, the compounds of the invention are considered useful for the prevention, treatment or inhibition of disorders or conditions such as convulsions, epilepsy, anxiety disorders, neuropathic pain and neurodegenerative disorders.

Accordingly, the compounds of the invention are considered useful in the prevention, treatment and inhibition of convulsions.

Accordingly, the compounds of the invention are considered useful in the prevention, treatment and inhibition of epilepsy, epileptic syndromes and epileptic seizures.

The compounds of the invention are further considered useful in the prevention, treatment and inhibition of anxiety disorders such as conditions and diseases related to panic attack, agoraphobia, panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorders, generalized anxiety disorder, anxiety disorder due to general medical condition, substance-induced anxiety disorder, separation anxiety disorder, adjustment disorders and anxiety disorder not otherwise specified.

The compounds of the invention are also considered useful in the prevention, treatment and inhibition of neuropathic pain such as allodynia, hyperalgesic pain, phantom pain, neuropathic pain related to diabetic neuropathie and neupathic pain related to migraine.

Additionally, the compounds of the invention are considered useful in the prevention, treatment and inhibition of neurodegenerative disorders such as alzheimer's disease; huntington's chorea; multiple sclerosis; amyotrophic lateral sclerosis; Creutzfeld-Jakob disease; Parkinson's disease; encephalopathies induced by AIDS or infection by rubella viruses, herpes viruses, borrelia and unknown pathogens; trauma-induced neurodegenerations; neuronal hyperexcitation states such as in medicament withdrawal or intoxication; and neurodegenerative diseases of the peripheral nervous system such as polyneuropathies and polyneuritides.

According to one particular aspect of the invention, the compounds are KCNQ2 active with an EC_{50} of less than 10000nM.

According to one particular aspect of the invention, the compounds are KCNQ2 active with an EC_{50} of less than 2000nM.

According to another particular aspect of the invention, the compounds are KCNQ2 active with an EC_{50} of less than 200nM.

Definitions

The term heteroatom refers to a nitrogen, oxygen or sulphur atom.

Halogen means fluoro, chloro, bromo or iodo.

The expressions C_{1-6}-alk(en/yn)yl and C_{1-6}-alk(an/en/yn)yl mean a C_{1-6}-alkyl, C_{2-6}-alkenyl or a C_{2-6}-alkynyl group.

The term C_{1-6}-alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, C_{2-6}-alkenyl and C_{2-6}-alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The expressions C_{1-4}-alkyl and C_{1-4}-alkanyl refer to a branched or unbranched alkyl group having from one to four carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

The expression C_{1-3}-alk(en/yn)yl means a C_{1-3}-alkyl, C_{2-3}-alkenyl or a C_{2-3}-alkynyl group.

The term C_{1-3}-alkyl refers to a branched or unbranched alkyl group having from one to three carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl and 2-propyl.

Similarly, C_{2-3}-alkenyl and C_{2-3}-alkynyl, respectively, designate such groups having from two to three carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, ethynyl and propynyl.

The expressions C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(an/en)yl mean a C_{3-8}-cycloalkyl- or cycloalkenyl group.

The term C_{3-8}-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The expressions C_{3-6}-cycloalk(en)yl and C_{3-6}-cycloalk(an/en)yl mean a C_{3-6}-cycloalkyl- or cycloalkenyl group.

The term C_{3-6}-cycloalkyl designates a monocyclic or bicyclic carbocycle having three to six C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term C_{3-8}-cycloalkenyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

The expression C_{5-8}-cycloalk(en)yl means a C_{5-8}-cycloalkyl- or cycloalkenyl group.

The term C_{5-8}-cycloalkyl designates a monocyclic or bicyclic carbocycle having five to eight C-atoms, including but not limited to cyclopentyl, cyclohexyl, etc.

The term C_{5-8}-cycloalkenyl designates a monocyclic or bicyclic carbocycle having five to eight C-atoms and including one or two double bonds.

In the term C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{1-6}-alk(en/yn)yl are as defined above.

The term Ar refers to optionally substituted aromatic systems of 5-10 carbon atoms, wherein 0, 1, 2, 3 or 4 carbon atoms may be replaced with independently selected heteroatoms. Examples of such Ar groups are optionally substituted phenyl, naphtyl, thiophene, furan thiazole and oxazole. Ar may be substituted with one or more substituents independently being hydroxy, halogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halo-C_{1-6}-alk(en/yn)yl, C_{1-6}-alk(an/en/yn)yloxy, C_{3-8}-alk(an/en/yn)yloxy, acyl or cyano, -CO-NH-C_{1-6}-

alk(en/yn)yl, -CO-N(C_{1-6}-alk(en/yn)yl)$_2$, -NH-C_{1-6}-alk(en/yn)yl, -N(C_{1-6}-alk(en/yn)yl)$_2$, -S- C_{1-6}-alk(en/yn)yl, -SO_2-C_{1-6}-alk(en/yn)yl and -SO_2O-C_{1-6}-alk(en/yn)yl; or two substituents may together form a 5-8 membered saturated or unsaturated ring which optionally contains one or two heteroatoms. Two ringforming substituents may be adjacent and may together form –$(CH_2)_{n**}$–CH_2-, -CH=CH-$(CH_2)_{m**}$-, -CH_2-CH=CH-$(CH_2)_{p**}$, –$(CH_2)_{n**}$–O-, –O-$(CH_2)_{m**}$–O-, -CH_2-O-$(CH_2)_{p**}$-O-, -CH_2-O-CH_2-O-CH_2-, –$(CH_2)_{n**}$–S-, –S-$(CH_2)_{m**}$–S-, -CH_2-S-$(CH_2)_{p**}$-S-, -CH_2-S-CH_2-S-CH_2-, –$(CH_2)_{n**}$–NH- , –NH-$(CH_2)_{m**}$–NH-, -CH_2-NH-$(CH_2)_{p**}$-NH-, – CH=CH-NH-, –O-$(CH_2)_{m**}$–NH-, -CH_2-O-$(CH_2)_{p**}$-NH- or -O-$(CH_2)_{p**}$-NH-CH_2-, -S-$(CH_2)_{m**}$-NH- , -N=CH-NH-, -N=CH-O- or -N=CH-S-, wherein m** is 1, 2 or 3, n** is 2, 3 or 4 and p** is 1 or 2.

As used herein, the term acyl refers to formyl, C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-cycloalk(en)ylcarbonyl, Ar-carbonyl, Ar-C_{1-6}-alk(en/yn)ylcarbonyl or a C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl-carbonyl group, wherein C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and Ar are as defined above.

The term halo-C_{1-6}-alk(en/yn)yl designates C_{1-6}-alk(en/yn)yl being substituted with one or more halogen atoms, including but not limited to trifluoromethyl.

The terms hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn), C_{1-6}-alk(an/en/yn)yloxy, C_{1-4}-alkanyloxy, C_{2-6}-alkenyloxy, C_{2-6}-alkynyloxy, C_{3-8}-alk(an/en/yn)yloxy, C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-alk(en/yn)ylcarbonyl, Ar-carbonyl, Ar-C_{1-6}-alk(en/yn)ylcarbonyl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)ylcarbonyl etc. designate such groups in which the C_{1-6}-alk(en/yn)yl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalk(en)yl and Ar are as defined above.

The term two substituents together form a 5-8 membered saturated or unsaturated ring, which optionally contains one or two heteroatoms, refers to aliphatic or aromatic carbocyclic or heterocyclic systems wherein the ring is formed by 5 to 8 atoms which may be substituted by one or more substituents independently being C_{1-6}-alk(en/yn)yl, C_{3-8}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, halogen, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-alk(en/yn)yl or C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl.

The salts of the invention are preferably pharmaceutically acceptable salts. Such salts include pharmaceutical acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts.

Acid addition salts include salts of inorganic acids as well as organic acids.

Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, sulfuric, sulfamic, phosphoric and nitric acids and the like.

Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, ethanesulfonic, tartaric, ascorbic, pamoic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, bis-methylenesalicylic, methanesulfonic, ethanedisulfonic, itaconic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline.and the like. Further examples of pharmaceutical acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci. 1977,66,2, which is incorporated herein by reference.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

Also intended as pharmaceutical acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers, as separated, pure or partially purified optical isomers or racemic mixtures thereof are included within the scope of the

invention.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

The compounds of this invention may exist in unsolvated as well as in solvated forms with solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention. Racemic forms can be resolved into the optical antipodes by known methods, for example, by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formulas I, XI, XII, XIII, XIV or XV, which are readily convertible in vivo into the required compound of the formulas I, XI, XII, XIII, XIV or XV. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

Whenever mentioned in relation to the compounds of the formulas I, XI, XII, XIII, XIV or XV, the terms epilepsy and epilepsies embrace any of the epilepsies, epileptic syndromes and epileptic seizures referred to in International League Against Epilepsy: Proposal for revised clinical and electroencephalographic classification of epileptic seizures. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* **1981** 22: 489-501 and in International League Against Epilepsy: Proposal for revised classification of epilepsies and epileptic syndromes. Commission on Classification and Terminology of the International League Against Epilepsy. *Epilepsia* **1989** 30(4): 389-399.

Whenever mentioned in relation to the compounds of the formulas I, XI, XII, XIII, XIV or XV, the term anxiety disorders embraces conditions and diseases related to panic attack, agoraphobia, panic disorder with agoraphobia, panic disorder without agoraphobia, agoraphobia without history of panic disorder, specific phobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, acute stress disorders, generalized anxiety disorder, anxiety disorder due to general medical condition, substance-induced anxiety disorder, separation anxiety disorder, adjustment disorders and anxiety disorder not otherwise specified as defined by American Psychiatric Association *Diagnostic and statistical manual of mental disorders*, 4ed 1994: 110-113, 393-444 and 623-627.

Pharmaceutical compositions

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

The pharmaceutical compositions of this invention or those which are manufactured in accordance with this invention may be administered by any suitable route, for example orally in the form of tablets, capsules, powders, syrups, etc., or parenterally in the form of solutions for injection. For preparing such compositions, methods well known in the art may be used, and any pharmaceutically acceptable carriers, diluents, excipients or other additives normally used in the art may be used.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.05 to about 1000 mg, preferably from about 0.1 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is a base addition salt of a compound having the utility of a free acid. When a compound of the invention contains a free acid such salts are prepared in a conventional manner by treating a solution or suspension of a free acid of the compound of the invention with a chemical equivalent of a pharmaceutically acceptable base. Representative examples are mentioned above.

For parenteral administration, solutions of the novel compounds of the invention in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to a desired volume, sterilising the solution and filling it in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents.

Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, agar, pectin, acacia, stearic acid and lower alkyl ethers of cellulose corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like.

Any other adjuvants or additives usually used for such purposes such as colourings, flavourings, preservatives etc. may be used provided that they are compatible with the active ingredients.

Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

The pharmaceutical compositions formed by combining the novel compounds of the invention and the pharmaceutical acceptable carriers are then readily administered in a

variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include one or more suitable excipients. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

If a solid carrier is used for oral administration, the preparation may be tablette, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge.

The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

If desired, the pharmaceutical composition of the invention may comprise the compound of the formulas I, XI, XII, XIII, XIV or XV in combination with further pharmacologically active substances such as those described in the foregoing.

Typical examples of recipes for the formulation of the invention are as follows:

1) Tablets containing 5.0 mg of a compound of the invention calculated as the free base:

Compound of formulas I, XI, XII, XIII, XIV or XV		5.0 mg
Lactose	60 mg	
Maize starch	30 mg	
Hydroxypropylcellulose	2.4 mg	

Microcrystalline cellulose	19.2 mg
Croscarmellose Sodium Type A	2.4 mg
Magnesium stearate	0.84 mg

2) Tablets containing 0.5 mg of a compound of the invention calculated as the free base:

Compound of formulas I, XI, XII, XIII, XIV or XV	0.5 mg
Lactose	46.9 mg
Maize starch	23.5 mg
Povidone	1.8 mg
Microcrystalline cellulose	14.4 mg
Croscarmellose Sodium Type A	1.8 mg
Magnesium stearate	0.63 mg

3) Syrup containing per millilitre:

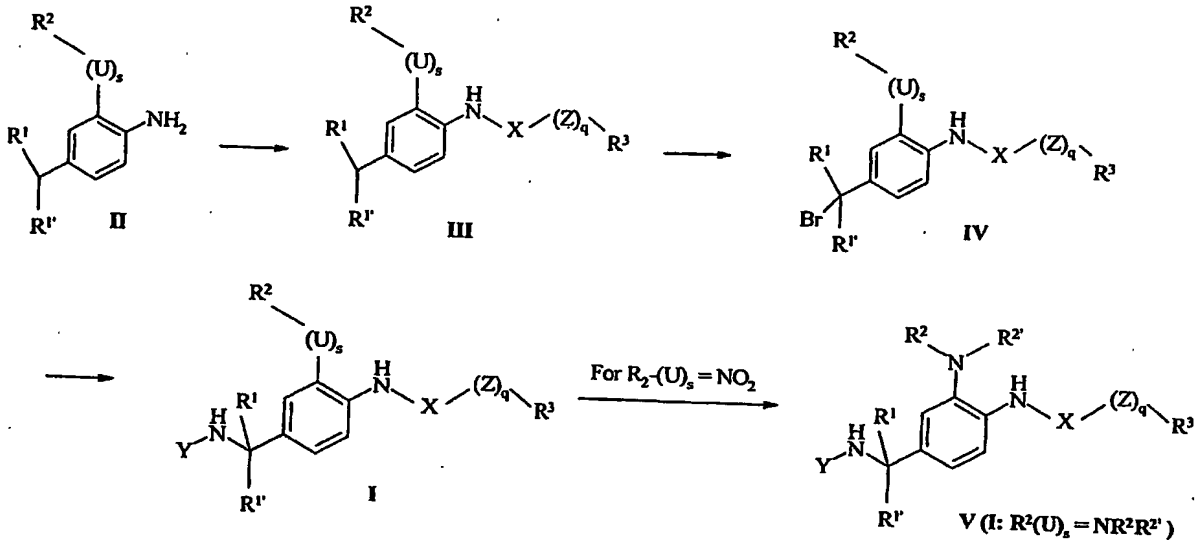
Compound of formulas I, XI, XII, XIII, XIV or XV	25 mg
Sorbitol	500 mg
Hydroxypropylcellulose	15 mg
Glycerol	50 mg
Methyl-paraben	1 mg
Propyl-paraben	0.1 mg
Ethanol	0.005 mL
Flavour	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 mL

4) Solution for injection containing per millilitre:

Compound of formulas I, XI, XII, XIII, XIV or XV	0.5 mg
Sorbitol	5.1 mg
Acetic Acid	0.05 mg
Saccharin sodium	0.5 mg
Water	ad 1 mL

Preparation of the compounds of the invention

The compounds of the invention of the general formula I, wherein R^1, $R^{1'}$, R^2, $R^{2'}$, R^3, U, Y, X, Z, q and s are as defined above are prepared by the methods as represented in the scheme and as described below:



Compounds of the general structure **II** are either obtained from commercial sources, or prepared by standard methods known to chemists skilled in the art.

Compounds of the general structure **III**, in which R^1 and $R^{1'}$ together are =O, are either obtained from commercial sources, or prepared by standard methods known to chemists skilled in the art as outlined below:

Carboxylic acids are reduced with appropriate reducing agents, such as borane, and carboxylic acid esters are reduced with appropriate reducing agents, such as diisobutyl aluminium hydride. The resulting benzylic alcohols are then reacted with a suitable oxidant, such as tetrapropylammonium perruthenate/N-methylmorpholin-N-oxide, pyridinium chlorochromat or dimethylsulfoxide/ oxalylchloride.

Additionally, for further variation of R^2, compounds of the general formula **III**, wherein R^2 = methyl, U = oxygen, and s = 1, can be demethylated by methods known

to chemists skilled in the art, such as treatment with boron tribromide in a suitable solvent, such as dichloromethane, at a suitable temperature, such as 0 °C or room temperature. The resulting phenols can then be transformed into compounds of the general formula **III**, wherein U = oxygen, and s = 1, by methods known to chemists skilled in the art. Such methods include: (a) the reaction with electrophiles, such as alkyl chlorides, alkyl bromides, alkyl iodides, benzyl chlorides, benzyl bromides, benzyl iodides, carbonic acid chlorides, carbonic acid bromides, or carbonic acid anhydrides in the presence of suitable bases, such as potassium carbonate, in a suitable solvent, such as tetrahydrofuran, *N,N*-dimethylformamide, or 1,2-dichloroethane, at suitable temperatures, such as room temperature or reflux temperature; (b) the reaction with alkyl, benzylic, or heteroarylalkyl alkohols under conditions known as the *Mitsunobu* reaction (O. Mitsunobu *Synthesis* **1981**, 1).

Alternatively, compounds of the general formula **III** are prepared by the reaction of compounds of the general structure **II** with suitable electrophilic reagents, such as suitably substituted acid chlorides, acid bromides, acid iodides, sulfonyl chlorides, carbamoyl chlorides, chloro formates, isocyanates and with or without the addition of bases, such as pyridine, trialkyl amines, potassium carbonate, or lithium-, sodium-, or potassium alcoholates, in a suitable solvent, such as ethyl acetate, dioxane, tetrahydrofuran, or diethyl ether, at a suitable temperature, such as room temperature or reflux temperature.

Compounds of the general formula **IV** are prepared from compounds of the general formula **III** by radical halogenation reactions known to the chemist skilled in the art, such as reaction with N-bromosuccinimide and dibenzoylperoxide, in a suitable solvent, such as tetrachloromethane or benzene at a suitable temperature, such as reflux temperature.

Compounds of the general formula **I** are prepared by reaction of compounds of the general formula **IV** with amines of type Y-NH_2, for example 4-tert-butylaniline, in a suitable solvent, such as tetrahydrofuran, dioxane or N,N-dimethylformamide, with or without addition of bases, such as trialkyl amines or potassium carbonate, at a suitable temperature.

Alternatively, compounds of the general formula **I** can be prepared by reductive amination reactions of compounds of the general formula **III** (R^1 and $R^{1'}$ together are =O), known to the chemist skilled in the art, with amines of type Y-NH_2, using reducing agents, such as sodium borohydride or sodium cyanoborohydride in a suitable solvent, such as methanol, ethanol, tetrahydrofuran, water, dioxane or mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid or hydrochloric acid, at a suitable temperature.

Alternatively, compounds of the general formula **III** (R^1 and $R^{1'}$ together are =O) can be reacted with amines of type Y-NH_2, in a suitable solvent, such as methanol, ethanol, tetrahydrofuran, dioxane, xylene or mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid, at a suitable temperature, to form imines, that can be isolated by crystallisation or by evaporation of the solvent. The imines can then be reduced using reducing agents, such as sodium borohydride or sodium cyanoborohydride in a suitable solvent, such as methanol, ethanol, tetrahydrofuran, water, dioxane or mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid, at a suitable temperature, to give compounds of the general formula **I**.

Compounds of the general formula **V**, where R^2 and $R^{2'}$ are hydrogen, are prepared by the reaction of compounds of the general formula **I**, where R_2-$(U)_s$ is NO_2, with a suitable reducing agent, such as iron or zinc powder in aqueous hydrochloric acid or aqueous sodium dithionite, in a suitable solvent, such as tetrahydrofuran.

To obtain compounds of the general formula **V**, where R^2 and optionally $R^{2'}$ are not hydrogen, a protecting group, such as ^{t}butyloxycarbonyl, is introduced at the benzylic nitrogen in compounds of the general formula **I**, before the reduction of the nitro group, by methods known to the chemist skilled in the art. This protecting group is cleaved by known methods after the introduction of R^2 and optionally $R^{2'}$ which is accomplished by using the following methods:

Introduction of R^2 by a reductive alkylation procedure using suitable aldehydes and reducing agents, such as sodium borohydride or sodium cyanoborohydride in a suitable solvent, such as methanol, ethanol, tetrahydrofuran, water, dioxane or

mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid, at a suitable temperature, as described above.

Optional introduction of $R^{2'}$ by an additional reductive alkylation procedure using suitable aldehydes and reducing agents, such as sodium borohydride or sodium cyanoborohydride in a suitable solvent, such as methanol, ethanol, tetrahydrofuran, water, dioxane or mixtures thereof, with or without addition of catalytic amounts of acid, such as acetic acid, at a suitable temperature, as described above.

Alternatively, $R^{2'}$ or R^2 is introduced by an acylation reaction using suitable electrophilic reagents, such as acid chlorides, acid bromides, acid iodides, sulfonyl chlorides, and alkyl formates with the addition of bases, such as trialkyl amines, potassium carbonate, or lithium-, sodium-, or potassium alcoholates, in a suitable solvent, such as ethyl acetate, dioxane, tetrahydrofuran, or diethyl ether, at a suitable temperature, as described above.

Examples

Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmmetry C18 column with 3.5 µm particle size; Solventsystem: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid (5:95:0.03); Method: Linear gradient elution with 90% A to 100% B in 4 min and with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace. The retention times (RT) are expressed in minutes.

^{1}H NMR spectra were recorded at 500.13 MHz and ^{13}C NMR spectra were recorded at 125.76 MHz, both on a Bruker Avance DRX500 instrument. Deuterated chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and b = broad singlet.

Preparation of intermediates

(4-Methyl-2-nitrophenyl)-carbamic acid ethyl ester

4-Methyl-2-nitroaniline (45.7 g, 0.30 mol) was dissolved in THF (350 ml) and K_2CO_3 (50 g, 0.36 mol) added. Ethyl chloroformate (39.1 g, 0.36 mol) dissolved in THF (50 ml) was added and the solution refluxed for 18 h. The mixture was cooled to ambient temperature and the solid filtered off. The solution was concentrated in vacuo and the resulting solid recrystallised from ethanol to give 47.1 g (70 %) of the title compound as yellow crystals. LC/MS (m/z) 224.9 (MH^+); RT = 3.08 min. ^1H NMR ($CDCl_3$): 1.35 (t, 3H); 2.38 (s, 3H); 4.28 (q, 2H); 7.42 (d, 1H); 8.00 (s, 1H); 8.45 (d, 1H); 9.70 (s, 1H). ^{13}C NMR ($CDCl_3$): 14.4, 20.4, 61.9, 120.7, 125.6, 132.4, 133.1, 135.9, 136.9, 153.3.

(4-Bromomethyl-2-nitrophenyl)-carbamic acid ethyl ester

(4-Methyl-2-nitrophenyl)-carbamic acid ethyl ester (22.4 g, 0.10 mol) is dissolved in CCl_4 (300 ml) and N-bromosuccinimide (17.8 g, 0.10 mmol) is added followed by dibenzoylperoxid (0.73 g, 0.003 mol). The mixture is stirred at reflux for 12 h and then cooled to ambient temperature. The mixture was filtered and the solution concentrated in vacuo. The remaining solid was recrystallised from methanol to give 17.0 g (56 %) of the title compound as bright yellow crystals. LC/MS (m/z) 304.3 (MH^+); RT = 3.22 min. ^1H NMR ($CDCl_3$): 1.38 (t, 3H); 4.29 (q, 2H); 4.50 (s, 2H); 7.65 (d, 1H); 8.25 (s, 1H); 8.58 (d, 1H); 9.85 (s, 1H). ^{13}C NMR ($CDCl_3$): 14.8, 31.5, 62.5, 121.6, 126.5, 132.4, 135.9, 136.0, 136.8, 153.4.

Preparation of intermediates of general structure I, where R^2-(U)s = NO_2

{4-[(4-tert-Butyphenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester

(4-Bromomethyl-2-nitrophenyl)-carbamic acid ethyl ester (0.5 g, 1.65 mmol), 4-tert-butyl-aniline (0.28 g, 1.8 mmol) and K_2CO_3 (0.35 g, 2.5 mmol) were mixed in THF (15 ml) and heated to reflux temperature for 12 h. The mixture was cooled to ambient temperature, filtered and evaporated to dryness in vacuo. Purified by chromatography using silica gel on a Flashmaster system eluting with heptane/ethyl acetate (linear gradient from 1:0 to 5:1). Fractions containing the product were pooled and evaporated in vacuo to yield the title compound (400 mg, 65 %).

LC/MS (m/z) 372.2 (MH^+); RT = 3.58 min, UV purity = 97.9, ELS purity = 98.1.

The following intermediates were prepared analogously:

(2-Nitro-4-phenylaminomethyphenyl)-carbamic acid ethyl ester

LC/MS (m/z) 315.0 (M^+); RT = 3.12 min, UV purity = 92.1, ELS purity = 95.0.

{2-Nitro-4-[(4-trifluoromethylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

LC/MS (m/z) 383.1 (MH^+); RT = 3.62 min, UV purity = 86.0, ELS purity = 98.2.

{4-[(4-Chlorophenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester

LC/MS (m/z) 349.1 (M^+); RT = 3.58 min, UV purity = 96.0, ELS purity = 98.7.

[4-(Naphthalen-2-ylaminomethyl)-2-nitrophenyl]-carbamic acid ethyl ester

LC/MS (m/z) 366.3 (MH^+); RT = 3.62 min, UV purity = 87.9, ELS purity = 92.3.

[2-Nitro-4-(p-tolylamino-methyl)-phenyl]-carbamic acid ethyl ester

LC/MS (m/z) 330.1 (MH^+); RT = 2.87 min, UV purity = 97.1, ELS purity = 98.4.

{4-[(3-Fluorophenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester

LC/MS (m/z) 332.0 (M^+); RT = 3.33 min, UV purity = 84.8, ELS purity = 96.1.

{4-[(4-Fluorophenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester

LC/MS (m/z) 332.0 (M^+); RT = 3.10 min, UV purity = 98.2, ELS purity = 98.8. ^1H NMR ($CDCl_3$): 1.33 (t, 3H); 4.00 (br s, 1H, NH); 4.28 (q, 2H); 4.33 (s, 2H); 6.52 (m, 2H); 6.88 (m, 2H); 7.65 (m, 1H); 8.20 (s, 1H); 8.55 (m, 1H); 9.78 (s, 1H, NH).

{4-[(2-Fluorophenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester

LC/MS (m/z) 333.8 (MH^+); RT = 3.41 min, UV purity = 93.8, ELS purity = 96.1.

[4-(Biphenyl-4-ylaminomethyl)-2-nitrophenyl]-carbamic acid ethyl ester

LC/MS (m/z) 392.3 (MH^+); RT = 3.74 min, UV purity = 87.0, ELS purity = 94.5.

{4-[(2,4-Difluorophenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester

LC/MS (m/z) 351.3 (M^+); RT = 3.45 min, UV purity = 96.1, ELS purity = 97.2.

{4-[(4-Methoxyphenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester
LC/MS (m/z) 346.1 (MH^+); RT = 2.16 min, UV purity = 87.3, ELS purity = 96.9.

{4-[(4-Cyclohexylphenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester
LC/MS (m/z) 397.2 (M^+); RT = 3.87 min, UV purity = 95.8, ELS purity = 98.6.

[4-(Indan-5-ylaminomethyl)-2-nitrophenyl]-carbamic acid ethyl ester
LC/MS (m/z) 355.2 (M^+); RT = 2.97 min, UV purity = 97.1, ELS purity = 99.2.

{4-[(4-Isopropylphenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester
LC/MS (m/z) 358.1 (MH^+); RT = 3.33 min, UV purity = 98.1, ELS purity = 99.3.

{4-[(4-Butylphenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester
LC/MS (m/z) 371.8 (M^+); RT = 3.10 min, UV purity = 92.3, ELS purity = 94.1.

Compounds of the invention

Example 1

1a {2-Amino-4-[(4-tert-butylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester
{4-[(4-tert-Butylphenylamino)-methyl]-2-nitrophenyl}-carbamic acid ethyl ester (400 mg, 1.08 mmol) was dissolved in THF (20 ml) and heated to 40 °C. Sodiumdithionite (1.13 g, 6.5 mmol) dissolved in water (20 ml) was added. The mixture was stirred vigorously at 40 °C until all starting material was consumed as judged by TLC. After cooling to ambient temperature brine (10 ml) is added and the mixture extracted with THF (2x15 ml). The combined organic phases are dried over $MgSO_4$, filtered and evaporated to dryness in vacuo. Purified by chromatography using silica gel on a Flashmaster system eluting with heptane/ethyl acetate (linear gradient from 1:0 to 4:1). Fractions containing the product were pooled and evaporated in vacuo to yield the title compound (230 mg, 62 %). LC/MS (m/z) 341.1 (M^+); RT = 2.12 min, UV purity = 97.8, ELS purity = 99.1. ^1H NMR ($CDCl_3$): 1.27 (s, 9H); 1.32 (t, 3H); 3.75 (br, 2H, NH_2; 3.80 (br s, 1H, NH); 4.22 (br m, 4H); 6.22 (br s, 1H, NH); 6.55 (d, 2H); 6.80 (m, 2H); 7.20 (br m, 3H).

The following compounds were prepared analogously:

1b (2-Amino-4-phenylaminomethyl-phenyl)-carbamic acid ethyl ester

LC/MS (m/z) 285.1 (M^+); RT = 1.46 min, UV purity = 98.2, ELS purity = 99.5. ^1H NMR ($CDCl_3$): 1.30 (t, 3H); 3.75 (br s, 2H, NH_2); 3.95 (br s, 1H, NH); 4.22 (br m, 4H); 6.25 (br s, 1H, NH); 6.60 (d, 2H); 6.72 (t, 1H); 6.82 (m, 2H); 7.15 (t, 2H); 7.22 (br m, 1H).

1c [2-Amino-4-(naphthalen-2-ylaminomethyl)-phenyl]-carbamic acid ethyl ester

LC/MS (m/z) 336.2 (MH^+); RT = 2.20 min, UV purity = 98.2, ELS purity = 99.4. ^1H NMR ($CDCl_3$): 1.31 (t, 3H); 3.80 (br, 3H, NH_2+NH); 4.25 (q, 2H); 4.35 (s, 2H); 6.25 (br s, 1H, NH); 6.82 (m, 3H); 6.92 (m, 1H); 7.18 (m, 1H); 7.22 (br m, 1H); 7.35 (m, 1H); 7.65 (br m, 3H).

1d [2-Amino-4-(p-tolylamino-methyl)-phenyl]-carbamic acid ethyl ester

LC/MS (m/z) 298.1 (M^+); RT = 1.50 min, UV purity = 98.3, ELS purity = 98.4. ^1H NMR ($CDCl_3$): 1.30 (t, 3H); 2.22 (s, 3H); 3.78 (br, 3H, NH_2+NH); 4.22 (br m, 4H); 6.25 (br s, 1H, NH); 6.55 (d, 2H); 6.80 (m, 2H); 6.98 (d, 2H); 7.21 (br m, 1H).

1e {2-Amino-4-[(4-trifluoromethylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

LC/MS (m/z) 353.1 (M^+); RT = 2.58 min, UV purity = 97.9, ELS purity = 99.2. ^1H NMR ($CDCl_3$): 1.30 (t, 3H); 3.76 (br s, 2H, NH_2); 4.23 (br m, 4H); 4.40 (br s, 1H, NH); 6.28 (br s, 1H, NH); 6.60 (d, 2H); 6.75 (m, 2H); 7.20 (br m, 1H); 7.40 (d, 2H).

1f {2-Amino-4-[(4-chlorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

LC/MS (m/z) 319.0 (MH^+); RT = 2.24 min, UV purity = 98.9, ELS purity = 98.7. ^1H NMR ($CDCl_3$): 1.31 (t, 3H); 3.76 (br s, 2H, NH_2); 4.00 (br s, 1H, NH); 4.22 (br m, 4H); 6.23 (br s, 1H, NH); 6.52 (d, 2H); 6.76 (m, 2H); 7.10 (d, 2H); 7.22 (br m, 1H).

1g {2-Amino-4-[(3-fluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

LC/MS (m/z) 303.1 (M^+); RT = 2.08 min, UV purity = 98.5, ELS purity = 99.9. ^1H NMR ($CDCl_3$): 1.32 (t, 3H); 3.75 (br s, 2H, NH_2); 4.15 (br s, 1H, NH); 4.24 (br m, 4H); 6.20 (br s, 1H, NH); 6.30 (m, 1H); 6.38 (m, 2H); 6.78 (m, 2H); 7.08 (m, 1H); 7.22 (br m, 1H).

1h {2-Amino-4-[(4-fluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester
LC/MS (m/z) 304.2 (M^+); RT = 1.58 min, UV purity = 96.1, ELS purity = 98.8. ^1H NMR ($CDCl_3$): 1.32 (t, 3H); 3.82 (br s, 3H, NH+NH_2); 4.18 (s, 2H); 4.23 (q, 2H); 6.25 (br s, 1H, NH); 6.52 (m, 2H); 6.77 (m, 2H); 6.88 (m, 2H); 7.20 (br m, 1H).

1i {2-Amino-4-[(2-fluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester
LC/MS (m/z) 303.0 (M^+); RT = 2.16 min, UV purity = 99.5, ELS purity = 99.8. ^1H NMR ($CDCl_3$): 1.30 (t, 3H); 3.75 (br s, 2H, NH_2); 4.21 (q, 2H); 4.28 (s, 2H); 4.38 (br s, 1H, NH); 6.30 (br s, 1H, NH); 6.63 (m, 2H); 6.70 (m, 2H); 6.95 (m, 2H); 7.20 (br m, 1H).

1j [2-Amino-4-(biphenyl-4-ylaminomethyl)-phenyl]-carbamic acid ethyl ester
LC/MS (m/z) 361.2 (M^+); RT = 2.45 min, UV purity = 97.0, ELS purity = 98.3. ^1H NMR ($CDCl_3$): 1.32 (t, 3H); 3.90 (br s, 3H, NH+NH_2); 4.21 (q, 2H); 4.30 (s, 2H); 6.25 (br s, 1H, NH); 6.70 (m, 2H); 6.82 (m, 2H); 7.25 (m, 2H); 7.37 (m, 2H); 7.44 m, 2H); 7.55 (m, 2H).

1k {2-Amino-4-[(2,4-difluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester
LC/MS (m/z) 320.1 (M^+); RT = 2.24 min, UV purity = 95.9, ELS purity = 99.9. ^1H NMR ($CDCl_3$): 1.31 (t, 3H); 3.75 (br s, 2H, NH_2); 4.12 (br s, 1H, NH); 4.23 (br m, 4H); 6.27 (br s, 1H, NH); 6.55 (m, 1H); 6.70 (m, 1H); 6.78 (m, 3H); 7.22 (br m, 1H).

1l {2-Amino-4-[(4-methoxyphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester
LC/MS (m/z) 314.9 (M^+); RT = 1.29 min, UV purity = 95.6, ELS purity = 99.9. ^1H NMR ($CDCl_3$): 1.31 (t, 3H); 3.72 (br m, 6H, OCH_3+NH+NH_2); 4.18 (s, 2H); 4.24 (q, 2H); 6.30 (br s, 1H, NH); 6.60 (d, 2H); 6.78 (br m, 4H); 7.21 (br m, 1H).

1m {2-Amino-4-[(4-cyclohexylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester
LC/MS (m/z) 366.9 (MH^+); RT = 2.45 min, UV purity = 96.2, ELS purity = 99.5. ^1H NMR ($CDCl_3$): 1.30 (br m, 9H); 1.82 (m, 4H); 2.40 (m, 1H); 3.78 (br, 3H, NH_2+NH); 4.22 (br m, 4H); 6.25 (br s, 1H, NH); 6.57 (d, 1H); 6.62 (d, 1H); 6.80 (m, 2H); 7.02 (m, 2H); 7.20 (br m, 1H).

1n [2-Amino-4-(indan-5-ylaminomethyl)-phenyl]-carbamic acid ethyl ester
LC/MS (m/z) 325.2 (MH^+); RT = 1.75 min, UV purity = 96.1, ELS purity = 98.4. ^1H NMR ($CDCl_3$): 1.30 (t, 3H); 2.02 (m, 2H); 2.80 (m, 4H); 3.75 (br, 3H, NH_2+NH); 4.22 (br m, 4H); 6.27 (br s, 1H, NH); 6.42 (d, 1H); 6.55 (s, 1H); 6.80 (m, 2H); 7.00 (d, 1H); 7.21 (br m, 1H).

1o {2-Amino-4-[(4-isopropylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester
LC/MS (m/z) 326.2 (MH^+); RT = 1.91 min, UV purity = 95.2, ELS purity = 98.5. ^1H NMR ($CDCl_3$): 1.20 (d, 6H), 1.32 (t, 3H); 2.80 (m, 1H); 3.75 (br, 3H, NH_2+NH); 4.22 (br m, 4H); 6.25 (br s, 1H, NH); 6.57 (d, 2H); 6.81 (m, 2H); 7.05 (d, 2H); 7.20 (br m, 1H).

1p {2-Amino-4-[(4-butylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester
LC/MS (m/z) 340.2 (M^+); RT = 2.16 min, UV purity = 97.2, ELS purity = 99.5. ^1H NMR ($CDCl_3$): 0.90 (t, 3H); 1.32 (m, 5H); 1.55 (m, 2H); 2.52 (t, 2H); 3.72 (br, 2H, NH_2); 3.88 (br, 1H, NH); 4.21 (br m, 4H); 6.22 (br s, 1H, NH); 6.56 (d, 2H); 6.80 (m, 2H); 6.98 (d, 2H); 7.20 (br m, 1H).

In vitro and in vivo testing

The compounds of the invention have been tested and shown effect in one or more of the below models:

Relative efflux through the KCNQ2 channel.

This exemplifies a KCNQ2 screening protocol for evaluating compounds of the present invention. The assay measures the relative efflux through the KCNQ2 channel, and was carried out according to a method described by Tang et al. (Tang, W. et. al., *J. Biomol. Screen.* **2001**, 6, 325-331) for hERG potassium channels with the modifications described below.

An adequate number of CHO cells stably expressing voltage-gated KCNQ2 channels were plated at a density sufficient to yield a mono-confluent layer on the day of the experiment. Cells were loaded with 1 µCi/ml [^{86}Rb] over night. On the day of the

experiment cells were washed with HBSS-containing buffer. Cells were pre-incubated with drug for 30 min. and the $^{86}Rb^{+}$ efflux was stimulated by 15 mM KCl in the continued presence of drug for additional 30 min. After the incubation period, the supernatant was removed and counted in a liquid scintillation counter (Tricarb). Cells were lysed with 2 mM NaOH and the amount of $^{86}Rb+$ was counted. The relative efflux was calculated $((CPM_{suoer}/CPM_{super}+ CPM_{cell})_{Cmpd}/ (CPM_{suoer}/CPM_{super}+ CPM_{cell})_{15mM\ KCl})*100-100$.

The compounds of the invention have an EC_{50} of less than 20000nM. Accordingly, the compounds of the invention are useful in the treatment of diseases associated with the KCNQ family potassium channels.

Electrophysiological patch-clamp recordings.

Voltage-activated KCNQ2 currents were recorded from mammalian CHO cells by use of conventional patch-clamp recordings techniques in the whole-cell patch-clamp configuration (Hamill OP et.al. *Pflügers Arch* **1981**; 391: 85-100). CHO cells with stable expression of voltage-activated KCNQ2 channels were grown under normal cell culture conditions in CO_2 incubators and used for electrophysiological recordings 1-7 days after plating. KCNQ2 potassium channels were activated by voltage steps up to + 80 mV in increments of 5-20 mV (or with a ramp protocol) from a membrane holding potential between – 100 mV and – 40 mV (Tatulian L et al. *J Neuroscience* **2001**; 21 (15): 5535-5545). The electrophysiological effects induced by the compounds were evaluated on various parameters of the voltage-activated KCNQ2 current. Especially effects on the activation threshold for the current and on the maximum induced current were studied.

Some of the compounds of the invention have been tested in this test. A left-ward shift of the activation threshold and/or an increase in the maximum induced potassium current is expected to decrease the activity in neuronal networks and thus make the compounds useful in diseases with increased neuronal activity - like epilepsia.

Maximum electroshock

The test was conducted in groups of male mice using corneal electrodes and administering a square wave current of 26mA for 0.4seconds in order to induce a

convulsion characterised by a tonic hind limb extension (Wlaz et al. *Epilepsy Research* **1998**, 30, 219-229).

Pilocarpine induced seizures

Pilocarpine induced seizures are induced by intraperitoneal injection of pilocarpine 250mg/kg to groups of male mice and observing for seizure activity resulting in loss of posture within a period of 30 minutes (Starr et al. *Pharmacology Biochemistry and Behavior* **1993**, 45, 321-325)

Pentylenetetrazole threshold test

The threshold dose of pentylenetetrazole required to induce a clonic convulsion was measured by timed infusion of pentylenetetrazole (5mg/ml at 0.5 ml/min) into a lateral tail vein of groups of male mice (Nutt et al. *J Pharmacy and Pharmacology* **1986**, 38, 697-698).

Side effects

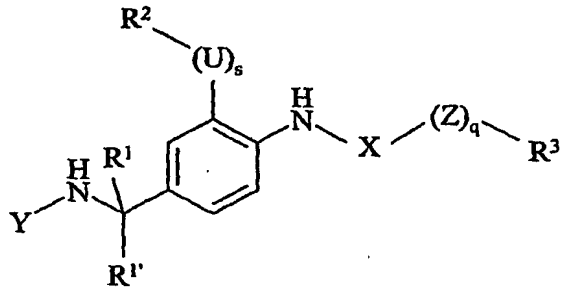
Central nervous system side-effects were measured by measuring the time mice would remain on rotarod apparatus (Capacio et al. *Drug and Chemical Toxicology* **1992**, 15, 177-201).

Pharmacokinetics

The pharmacokinetic properties of the compound were determined via. i.v. and p.o. dosing to Spraque Dawley rats, and, thereafter, drawing blood samples over 20 h. Plasma concentrations were determined with LC/MS/MS.

Claims

1. A substituted aniline derivative of formula I



(I)

wherein

U is O, S or $NR^{2'}$;

s is 0 or 1;

X is CO or SO_2;

Z is O, S or NR^4, wherein R^4 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

q is 0 or 1;

R^1 and $R^{1'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl;

R^2 is selected from the group consisting of hydrogen, halogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-

C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl and cyano; provided that when R^2 is halogen or cyano then s is 0;

when s is 1 and U is $NR^{2'}$ then $R^{2'}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl; or R^2 and $R^{2'}$ together form a 5-8 membered saturated or unsaturated ring which optionally contains one further heteroatom;

R^3 is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl;

and

Y represents a group of formula VI, VII, VIII, IX or X:

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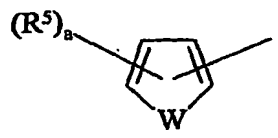

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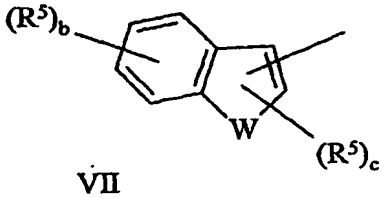

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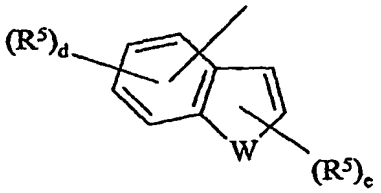
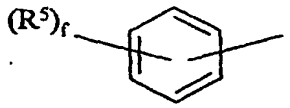
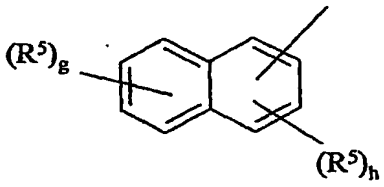


VIII



IX



X

wherein

the line represents a bond attaching the group represented by Y to the nitrogen atom;

W is O or S;

a is 0, 1, 2 or 3;

b is 0, 1, 2, 3 or 4;

c is 0 or 1;

d is 0, 1, 2 or 3;

e is 0, 1 or 2;

f is 0, 1, 2, 3, 4 or 5;

g is 0, 1, 2, 3 or 4;

h is 0, 1, 2 or 3; and

each R^5 is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(an/en/yn)yloxy, halogen, halo-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, nitro, -$NR^7R^{7'}$, -S-R^8, -SO_2R^8 and SO_2OR^8, or two substituents together form a 5-8 membered saturated or unsaturated ring which optionally contains one or two heteroatoms;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar;

R^7 and $R^{7'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and acyl; and

R^8 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and $-NR^9R^{9'}$; wherein R^9 and $R^{9'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; with the provisos that when R^5 is SO_2OR^8 then R^8 is not $-NR^9R^{9'}$ and when R^5 is SO_2R^8 then R^8 is not a hydrogen atom.

or salts thereof.

2. A compound according to Claim 1, wherein at least one of R^1 and $R^{1'}$ is a hydrogen atom.

3. A compound according to any of Claims 1-2, wherein both R^1 and $R^{1'}$ are hydrogen atoms.

4. A compound according to any of Claims 1-3, wherein s is 1.

5. A compound according to any of Claims 1-4, wherein U is $NR^{2'}$.

6. A compound according to any of Claims 1-5, wherein $R^{2'}$ is a hydrogen atom.

7. A compound according to any of Claims 1-6, wherein both R^2 and $R^{2'}$ are hydrogen atoms.

8. A compound according to any of Claims 1-9, wherein X is CO.

9. A compound according to any of Claims 1-8, wherein q is 1.

10. A compound according to any of Claims 1-9, wherein Z is O.

11. A compound according to any of Claims 1-10, wherein R^3 is C_{1-6}-alk(en/yn)yl.

12. A compound according to any of Claims 1-11, wherein each R^5 is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar, halogen, halo-C_{1-6}-alk(en/yn)yl and C_{1-6}-alk(an/en/yn)yloxy or two adjacent substituents together form a 5-8 membered saturated or unsaturated ring which optionally contains one or two heteroatoms.

13. A compound according to any of Claims 1-12, said compound being selected from the group consisting of:

1a {2-Amino-4-[(4-tert-butylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1b (2-Amino-4-phenylaminomethyl-phenyl)-carbamic acid ethyl ester

1c [2-Amino-4-(naphthalen-2-ylaminomethyl)-phenyl]-carbamic acid ethyl ester

1d [2-Amino-4-(p-tolylamino-methyl)-phenyl]-carbamic acid ethyl ester

1e {2-Amino-4-[(4-trifluoromethylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1f {2-Amino-4-[(4-chlorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1g {2-Amino-4-[(3-fluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1h {2-Amino-4-[(4-fluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1i {2-Amino-4-[(2-fluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1j [2-Amino-4-(biphenyl-4-ylaminomethyl)-phenyl]-carbamic acid ethyl ester

1k {2-Amino-4-[(2,4-difluorophenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1l {2-Amino-4-[(4-methoxyphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1m {2-Amino-4-[(4-cyclohexylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

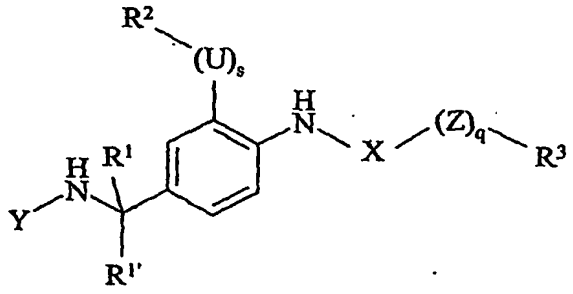
1n [2-Amino-4-(indan-5-ylaminomethyl)-phenyl]-carbamic acid ethyl ester

1o {2-Amino-4-[(4-isopropylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

1p {2-Amino-4-[(4-butylphenylamino)-methyl]-phenyl}-carbamic acid ethyl ester

or a salt thereof.

14. A pharmaceutical composition comprising one or more pharmaceutically acceptable carriers or diluents and a compound of the below formula I



(I)

wherein

U is O, S or $NR^{2'}$;

s is 0 or 1;

X is CO or SO_2;

Z is O, S or NR^4, wherein R^4 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

q is 0 or 1;

R^1 and $R^{1'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl;

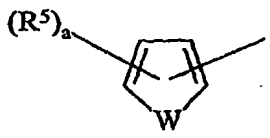
R^2 is selected from the group consisting of hydrogen, halogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl and cyano; provided that when R^2 is halogen or cyano then s is 0;

when s is 1 and **U** is $NR^{2'}$ then $R^{2'}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl; or R^2 and $R^{2'}$ together form a 5-8 membered saturated or unsaturated ring which optionally contains one further heteroatom;

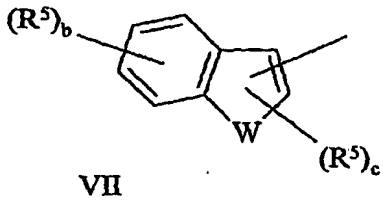
R^3 is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl;

and

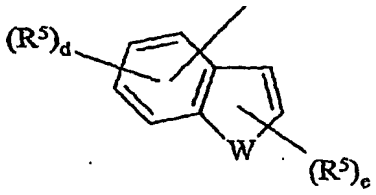
Y represents a group of formula VI, VII, VIII, IX or X:



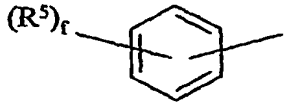
VI



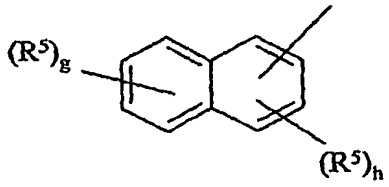
VII



VIII



IX



X

wherein

the line represents a bond attaching the group represented by Y to the nitrogen atom;

W is O or S;

a is 0, 1, 2 or 3;

b is 0, 1, 2, 3 or 4;

c is 0 or 1;

d is 0, 1, 2 or 3;

e is 0, 1 or 2;

f is 0, 1, 2, 3, 4 or 5;

g is 0, 1, 2, 3 or 4;

h is 0, 1, 2 or 3; and

each R^5 is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(an/en/yn)yloxy, halogen, halo-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, nitro, -$NR^7R^{7'}$, -S-R^8, -SO_2R^8 and SO_2OR^8, or two substituents together form a 5-8 membered saturated or unsaturated ring which optionally contains one or two heteroatoms;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar;

R^7 and $R^{7'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and acyl; and

R^8 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and $-NR^9R^{9'}$; wherein

R^9 and $R^{9'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; with the provisos that when R^5 is SO_2OR^8 then R^8 is not $-NR^9R^{9'}$ and when R^5 is SO_2R^8 then R^8 is not a hydrogen atom;

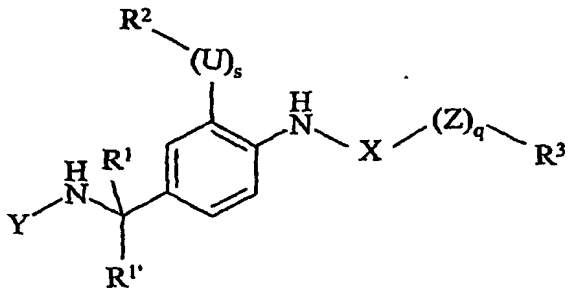
or salts thereof.

15. Use of a pharmaceutical composition according to Claim 14 for increasing ion flow in a potassium channel.

16. Use of a pharmaceutical composition according to Claim 15 for the prevention, treatment or inhibition of a disorder or condition being responsive to an increased ion flow in a potassium channel.

17. Use according to Claim 16, wherein said disorder or condition is selected from the group consisting of convulsions epilepsy, anxiety disorders, neuropathic pain and neurodegenerative disorders.

18. A method of increasing ion flow in a potassium channel, comprising administering a therapeutically effective amount of a compound of formula I



(I)

wherein

U is O, S or $NR^{2'}$;

s is 0 or 1;

X is CO or SO_2;

Z is O, S or NR^4, wherein R^4 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, hydroxy-C_{1-6}-alk(en/yn)yl and hydroxy-C_{3-8}-cycloalk(en)yl;

q is 0 or 1;

R^1 and $R^{1'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl;

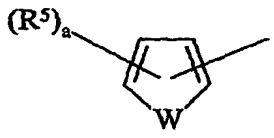
R^2 is selected from the group consisting of hydrogen, halogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl, halo-C_{3-8}-cycloalk(en)yl and cyano; provided that when R^2 is halogen or cyano then s is 0;

when s is 1 and U is $NR^{2'}$ then $R^{2'}$ is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, acyl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl; or R^2 and $R^{2'}$ together form a 5-8 membered saturated or unsaturated ring which optionally contains one further heteroatom;

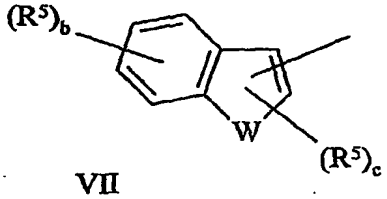
R^3 is selected from the group consisting of C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar, Ar-C_{1-6}-alk(en/yn)yl, Ar-C_{3-8}-cycloalk(en)yl, hydroxy-C_{1-6}-alk(en/yn)yl, hydroxy-C_{3-8}-cycloalk(en)yl, halo-C_{1-6}-alk(en/yn)yl and halo-C_{3-8}-cycloalk(en)yl;

and

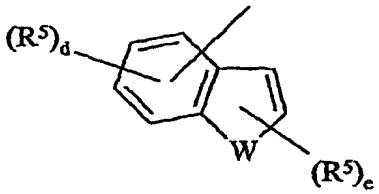
Y represents a group of formula VI, VII, VIII, IX or X:



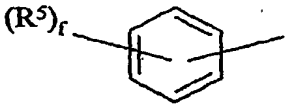
VI



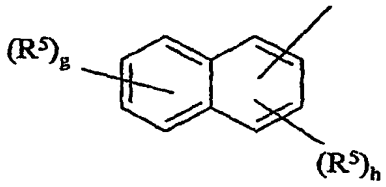
VII



VIII



IX



X

wherein

the line represents a bond attaching the group represented by Y to the nitrogen atom;

W is O or S;

a is 0, 1, 2 or 3;

b is 0, 1, 2, 3 or 4;

c is 0 or 1;

d is 0, 1, 2 or 3;

e is 0, 1 or 2;

f is 0, 1, 2, 3, 4 or 5;

g is 0, 1, 2, 3 or 4;

h is 0, 1, 2 or 3; and

each R^5 is independently selected from the group consisting of a C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, Ar, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar-C_{1-6}-alk(en/yn)yl, acyl, C_{1-6}-alk(an/en/yn)yloxy, halogen, halo-C_{1-6}-alk(en/yn)yl, -CO-$NR^6R^{6'}$, cyano, nitro, -$NR^7R^{7'}$, -S-R^8, -SO_2R^8 and SO_2OR^8, or two substituents together form a 5-8 membered saturated or unsaturated ring which optionally contains one or two heteroatoms;

R^6 and $R^{6'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl and Ar;

R^7 and $R^{7'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and acyl; and

R^8 is selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl, C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl, Ar and $-NR^9R^{9'}$; wherein R^9 and $R^{9'}$ are independently selected from the group consisting of hydrogen, C_{1-6}-alk(en/yn)yl, C_{3-8}-cycloalk(en)yl and C_{3-8}-cycloalk(en)yl-C_{1-6}-alk(en/yn)yl; with the provisos that when R^5 is SO_2OR^8 then R^8 is not $-NR^9R^{9'}$ and when R^5 is SO_2R^8 then R^8 is not a hydrogen atom;

or salts thereof.

19. Use of a pharmaceutical composition according to Claim 18 for increasing ion flow in a potassium channel.

20. A method according to claim 19 for the prevention, treatment or inhibition of a disorder or condition responsive to an increased ion flow in potassium channel.

21. A method according to claim 20, wherein said disorder or condition is selected from the group consisting of convulsions, epilepsy, anxiety disorders, neuropathic pain and neurodegenerative disorders.